DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-061/ S-008, S-009, S-012
NDA 21-062/ S-009, S-010, S-012

Bristol Myers-Squibb Company
Attention: Joan Fung-Tomc, Ph.D.
Director, Regulatory Science
5 Research Parkway
P. O. Box 5100
Wallingford, CT 06492-7660

31 OCT 2001

Dear Dr. Fung-Tomc:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Product	NDA Number	Supplement Number	Date of Supplement	Date of Receipt
Tequin® (gatifloxacin) Tablets, 200 mg and 400 mg	21-061	S-008	June 22, 2001	June 25, 2001
		S-009	June 25, 2001	June 26, 2001
		S-012	August 30, 2001	August 31, 2001
Tequin® (gatifloxacin) Injection, 200 mg and 400 mg	21-062	S-009	June 22, 2001	June 25, 2001
		S-010	June 25, 2001	June 26, 2001
		S-012	August 30, 2001	August 31, 2001

We acknowledge receipt of your submissions to each supplement dated August 24, 2001 and October 18, 2001.

These supplemental new drug applications provide for the following changes to the Tequin® label. The deleted text is noted by ~~strikethrough~~ and the added text is noted by <u>double underline</u> as follows:

1. **CLINICAL PHARMACOLGY**

- In the **Glucose Homeostasis** subsection, the first paragraph was revised to read:

> ~~As with other quinolones, clinical experience has shown that d~~<u>D</u>isturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported ~~in patients treated concomitantly TEQUIN and other oral hypoglycemic agents with or without insulin,~~ with TEQUIN <u>(as with other quinolones), usually in diabetic patients.</u>
> Therefore, careful monitoring of blood glucose is recommended when TEQUIN is administered to ~~diabetic~~ patients ~~receiving treatment with oral hypoglycemic agents with or without insulin~~ <u>with diabetes.</u> (See **PRECAUTIONS: General, Information for Patients,** and **Drug Interactions**.)

- In the **Microbiology** subsection, the MIC breakpoint for *Haemophilus* was changed from ≤ 0.5 ug/mL to ≤ 1.0 ug/mL as follows:

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*[a]:

MIC (µg/mL)	**Interpretation**
≦1.0 ~~0.5~~	Susceptible (S)

2. **WARNINGS**

The first sentence in the next to the last paragraph in this section was revised to read:

~~Although not seen in clinical trials of TEQUIN, r~~Ruptures of the shoulder, hand, and Achilles tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones.

3. **PRECAUTIONS**

- In the **General** subsection, the following sentence was added before the last paragraph**:**

Because a hypotonic solution results, Water for Injection should not be used as a diluent when preparing a 2 mg/mL solution from the concentrated solution of gatifloxacin (10 mg/mL) (see **DOSAGE AND ADMINISTRATION**).

- In the **General** subsection, the last paragraph was revised to read:

~~As with other quinolones, d~~Disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported with TEQUIN (as with other quinolones), usually in diabetic patients~~. receiving concomitant treatment with oral hypoglycemic agents (e.g., glyburide) with or without insulin. In these patients, t~~The careful monitoring of blood glucose is recommended when TEQUIN is administered to patients with diabetes. If a hypoglycemic reaction ~~occurs in~~ or signs and symptoms of hyperglycemia occur in any patient being treated with TEQUIN, appropriate therapy should be initiated immediately and TEQUIN should be discontinued. (See **CLINICAL PHARMACOLOGY, PRECAUTIONS: Drug Interactions**, and **ADVERSE REACTIONS.)**

- In the **Information for Patients** subsection, the twelfth bullet was revised to read:

- that~~ if they are diabetic~~ disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported ~~in patients treated concomitantly~~ with TEQUIN (as with other quinolones ~~and oral hypoglycemic agents with or without insulin~~), usually in diabetic patients. If a hypoglycemic reaction ~~occurs, they~~ or symptoms of hyperglycemia occur, patients should initiate appropriate therapy immediately, discontinue TEQUIN, and contact a physician (see **PRECAUTIONS: General** and **Drug Interactions**).

4. **ADVERSE REACTIONS**

A **Postmarketing Adverse Event Reports** subsection was added to the end of this section to read:

The following events have been reported during postapproval use of TEQUIN. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Acute allergic reaction including anaphylactic reaction and angioneurotic edema, hepatitis, increased International Normalized Ratio (INR)/ prothrombin time, severe hyperglycemia (including hyperosmolar nonketotic hyperglycemia), severe hypoglycemia, tendon rupture, thrombocytopenia, and torsades de pointes.

5. **DOSAGE AND ADMINISTRATION**

- The **Intravenous Administration, *Compatible Intravenous solutions*** subsection was revised to read:

Because a hypotonic solution results, Water for Injection should not be used as a diluent when preparing a 2 mg/mL solution from the concentrated solution of gatifloxacin (10 mg/mL) (see **PRECAUTIONS**). Any of the following intravenous solutions may be used to prepare a 2 mg/mL gatifloxacin solution:

5% Dextrose Injection, USP
0.9% Sodium Chloride Injection, USP
5% Dextrose and 0.9% Sodium Chloride Injection, USP
Lactated Ringer's and 5% Dextrose Injection, USP
5% Sodium Bicarbonate Injection, USP
Plasma-Lyte® 56 and 5% Dextrose Injection (Multiple Electrolytes and Dextrose Injection, Type 1, USP)
M/6 Sodium Lactate Injection, USP
~~Water for Injection, USP~~

6. **Patient Package Insert**

- The third bullet under "**What about other medications I am taking?"** was revised to read:

If you have diabetes, it is important to let your healthcare provider know ~~if you are on oral hypoglycemic agents with or without insulin~~ that you have this condition and what medications you are taking for it.

- The third paragraph under "**What are the possible side effects of Tequin**?" was revised to read:

~~If you have diabetes, you should know that d~~Disturbances of blood sugar, including symptoms ~~of~~ high blood sugar (hyperglycemia) and low blood sugar (hypoglycemia), have been reported ~~in patients treated concomitantly~~ with TEQUIN (as with other quinolone antibiotics), ~~and oral antidiabetic drugs with or without insulin~~ usually in diabetic patients. If you develop ~~symptoms of~~ low blood sugar while on TEQUIN, you should take immediate measures to increase your blood sugar, stop taking TEQUIN, and contact your healthcare professional at once. If you develop high blood sugar while on TEQUIN, you should stop taking TEQUIN, and contact your healthcare professional at once. If you have diabetes or suspect that you may have diabetes, discuss how to detect changes in your blood sugar with your healthcare professional.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text and with the minor editorial revisions listed below. Accordingly, these supplemental applications are approved effective on the date of this letter.

1. Delete the word "including" stated twice in the first sentence in the twelvth bullet under **Information for Patients**.

2. Replace the word "mediations" with the word "medications" in the third bullet under "**What about other medications I am taking?"** in the Patient Package Insert.

3. Correct punctuation for the references in parenthesis. For example,

   ...TEQUIN is administered to patients with diabetes. (See **PRECAUTIONS: General, Information for Patients,** and **Drug Interaction.**)

   should read:

   ...TEQUIN is administered to patients with diabetes (See **PRECAUTIONS: General, Information for Patients,** and **Drug Interaction**).

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted October 18, 2001) and include the minor editorial revisions indicated.

Please submit the copies of final printed labeling (FPL) electronically to each application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplements NDA 21-061/S-008, S-009, S-012, NDA 21-062/S-009, S-010, S-012." Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Robin Anderson, Labeling Reviewer, at (301) 827-2127.

Sincerely,

Renata Albrecht, M. D.
Acting Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research